



Kunutsor, S. K., & Laukkanen, J. A. (2016). Gamma-glutamyltransferase and risk of prostate cancer: Findings from the KHD prospective cohort study. *International Journal of Cancer*.
<https://doi.org/10.1002/ijc.30511>

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Research Article: Cancer Epidemiology

Gamma-glutamyltransferase and risk of prostate cancer: findings from the KIH prospective cohort study

Running Title: GGT and prostate cancer risk

Setor K. Kunutsor¹ and Jari A. Laukkanen^{2,3}

¹School of Clinical Sciences, University of Bristol, Learning & Research Building (Level 1), Southmead Hospital, Southmead Road, Bristol, UK

²Institute of Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio, Finland.

³Central Finland Central Hospital, Jyväskylä, Finland

***Correspondence to:** Setor K. Kunutsor, School of Clinical Sciences, University of Bristol, Learning & Research Building (Level 1), Southmead Hospital, Southmead Road, Bristol, BS10 5NB, UK. Phone: +44-7539589186; Fax: +44-1174147924; Email address: skk31@cantab.net

Key words: Gamma-glutamyltransferase; risk factor; prostate cancer

Novelty and Impact

The prospective evidence on the association between gamma-glutamyltransferase (GGT) and prostate cancer risk has not been well studied and is not very clear. In this population-based prospective cohort study involving middle-aged Caucasian men, GGT was positively, nonlinearly, and independently associated with future prostate cancer risk. The association did not importantly vary across several clinical subgroups. Further study is needed to evaluate if GGT assays may have any potential relevance in the prevention of prostate cancer.

Abbreviations

Body mass index (BMI)

Confidence interval (CI)

C-reactive protein (CRP)

Fasting plasma glucose (FPG)

Finnish Cancer Registry (FCR).

Gamma glutamyltransferase (GGT)

Hazard ratios (HR)

High-density lipoprotein cholesterol (HDL-C)

Kuopio Ischemic Heart Disease (KIHD)

Regression dilution ratio (RDR)

Reactive oxygen species (ROS)

Socioeconomic status (SES)

Abstract

Increased circulating serum gamma-glutamyltransferase (GGT) has been linked with an increased risk of chronic disease outcomes, including overall and several site-specific cancers. However, the relationship of GGT with prostate cancer risk is uncertain. We aimed to assess the prospective association of GGT with risk of prostate cancer. Serum GGT activity was assessed at baseline in the Finnish Kuopio Ischemic Heart Disease prospective cohort of 2,390 men aged 42-61 years without a history of cancer at baseline. We corrected for within-person variability in GGT values using data from repeat measurements taken several years apart. During a median follow-up of 24.6 years, 230 cases of prostate cancer occurred. The age-adjusted regression dilution ratio for \log_e GGT was 0.69 [95% confidence interval (CI): 0.63-0.74]. Serum GGT was nonlinearly associated with risk of prostate cancer. In age-adjusted Cox regression analysis, the hazard ratio (HR) (95% CIs) for prostate cancer in a comparison of the top quartile versus bottom quartiles 1-3 of GGT values was 1.43 (1.07 to 1.93; $P=0.017$), which persisted on adjustment for several established cancer risk factors 1.46 (1.06 to 2.02; $P=0.020$). The association remained unchanged on further adjustment for total energy intake, socioeconomic status, physical activity, and C-reactive protein. The association did not importantly vary across several clinical subgroups. Gamma-glutamyltransferase is positively and independently associated with future risk of prostate cancer in a middle-aged Finnish male population over long-term follow-up. Further research is needed to understand the mechanistic pathways involved and if GGT may have potential relevance in prostate cancer prevention.

Prostate cancer is the second most common male cancer and it is the second leading cause of death from cancer in men. Despite a progressive decline in attributable deaths due to prostate cancer over the past decade due to major advances in its treatment and prevention, the absolute number of prostate cancer cases is expected to increase because of the ageing population. Prostate cancer therefore remains a vast public health problem. Established risk factors for prostate cancer include race, age, and family history.¹⁻³ Hereditary factors as well as environmental factors such as infections, diet, and hormonal changes, are also involved in the pathogenesis of prostate cancer.² Though these factors explain a large proportion of the risk of prostate cancer, its pathogenesis is still not fully established as several other potential risk factors appear to be involved. There is therefore a need to critically evaluate putative risk factors that may increase our knowledge of prostate cancer development, may have causal or predictive significance, and which will help develop preventive and management strategies. Experimental, mechanistic, and observational evidence suggests that chronic inflammation^{2,4} and oxidative stress⁵ play a role in the aetiopathogenesis of prostate cancer. Gamma-glutamyltransferase (GGT), an index of liver injury and used as a clue for excessive alcohol consumption,⁶ has been shown to be positively associated with chronic disease outcomes including cardiovascular disease (CVD), overall and several site-specific cancers.⁷⁻¹² Common pathways implicated to underlie the associations between GGT and these adverse disease outcomes are via the pro-oxidant and pro-inflammatory properties of GGT.¹³ Since similar pathways have been implicated for the development of prostate cancer,^{2,4} we hypothesized that GGT will be associated with an increased risk of prostate cancer. Though several large-scale prospective studies have demonstrated associations between GGT and several site-specific cancers,⁸ there is limited evidence on the nature and magnitude of the association of GGT with prostate cancer. In a large Swedish cohort, Van Hemelrijck and colleagues found evidence of associations between elevated GGT and risk of various site-specific cancers; however, clear evidence of an independent association between GGT and prostate cancer risk could not be demonstrated in this study.¹⁴ Given the limited data on the relationship between

GGT and prostate cancer, we sought to evaluate in detail, the shape, nature, and magnitude of the prospective association of GGT with risk of prostate cancer, using a population-based cohort of 2,390 apparently healthy cancer-free men from eastern Finland. Serial measurements of GGT were performed in a subset of participants to help quantify within-person variability in GGT values.

Materials and Methods

Study population

The study population were participants in the Kuopio Ischemic Heart Disease (KIHD) risk factor study, a prospective population-based cohort study designed to investigate risk factors for vascular disease and other chronic outcomes. The study design and recruitment methods have been described in detail previously.¹⁵ Briefly, participants were a representative sample of men aged 42-61 years living in the city of Kuopio and its surrounding rural communities in eastern Finland at the time of baseline examinations. There were 3,433 potentially eligible and randomly selected men; and of this number, 2,682 (78%) volunteered to participate; 186 did not respond to the invitation and 367 declined to give informed consent. Baseline examinations were performed between March 1984 and December 1989. The present analysis included a cohort of 2,390 cancer-free men at baseline, with complete information on GGT, relevant confounders, and incident prostate cancer cases. The study was approved by the Research Ethics Committee of the University of Eastern Finland and each participant provided written informed consent.

Measurement of risk markers

Collection of blood specimens and biochemical and lipid measurements have been described previously.¹⁶ Briefly, participants fasted overnight, were instructed to abstain from drinking alcohol for at least 3 days, and refrain from smoking for at least 12 h prior to assessment. Blood samples were taken in the morning and the serum samples were stored frozen at -80 °C before analyses. Serum GGT activity was measured using the kinetic method (Thermo Fisher Scientific, Vantaa, Finland) with repeat measurements

performed 4 years and 11 years after the baseline measurements in a random subset of participants as described previously.^{7, 17, 18} Fasting plasma glucose (FPG) was measured by the glucose dehydrogenase method (Merck, Darmstadt, Germany). C-reactive protein (CRP) with an immunometric assay (Immulite High Sensitivity C-Reactive Protein Assay; DPC, Los Angeles, CA, USA). Smoking, blood pressure, and total energy intake were assessed as described previously.^{16, 19} Alcohol consumption was assessed with a structured quantity–frequency method using the Nordic Alcohol Consumption Inventory.²⁰ Socioeconomic status (SES) was measured as a summary index that combined measures of occupation, occupational prestige, education, income, material standard of living and housing conditions. A high value on the SES index indicated a low socioeconomic state. The energy expenditure of physical activity was assessed using the validated KIHD 12-month leisure-time physical activity questionnaire.^{21, 22}

Ascertainment of prostate cancer cases

Ascertainment of prostate cancer cases has been described in detail in previous reports.^{23, 24} Briefly, all incident cases of prostate cancer that occurred from study enrollment through 2014 were included in the present analysis. Cases were derived from the population-based Finnish Cancer Registry (FCR). Every diagnosed cancer case in the health care system has been reported in a countrywide and population-based manner in Finland since 1953. The coverage of FCR is complete and there were no losses to follow-up.²⁵ The FCR file containing personal identity codes is annually matched through computerized linkage with the national cause of death register at Statistics Finland. Annual follow-up for cancer was done automatically using the personal identifiers. The FCR is regularly linked with the Central Population Register to ensure that the personal identity codes are correct. No cases of prostate cancer were diagnosed within the first six years of follow-up. All prostate cancer cases were histologically verified.²⁶

Statistical analysis

Log transformation was conducted for all skewed variables (GGT, CRP, and triglycerides) to approximate

normal distributions. Descriptive analyses were performed to summarize the baseline characteristics of the participants. Multivariate Cox proportional hazard regression models were used after confirming assumptions of proportionality of hazards. To quantify and correct for within-person variability in values of GGT, adjusted regression dilution ratios (RDRs) were estimated by regressing available repeat measurements on baseline values,²⁷ as described in previous reports.^{7, 17, 18} To assess the shape of the association between GGT and prostate cancer risk, hazard ratios (HRs) confidence intervals (CIs) using floating absolute risks,²⁶ were calculated within quartiles of baseline GGT values and plotted against mean GGT values within each quartile. This was to allow for comparisons across the groups irrespective of the arbitrarily chosen reference category (bottom quartile). As the association showed a nonlinear shape, GGT was not modelled continuously, but entered as categories (quartiles) defined according to its baseline distribution. Because of the relatively flat risk of prostate cancer across quartiles 1-3 of serum GGT values, these categories were combined and served as the reference comparison.. HRs were adjusted progressively for (i) age; (ii) body mass index (BMI), smoking status, history of diabetes mellitus, FPG, triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDL-C), and alcohol consumption; and (iii) total energy intake, SES, physical activity, and CRP. Given the high CVD mortality rate in the KIID cohort, we also performed additional analyses to estimate the baseline cumulative subhazard of prostate cancer considering CVD death as a competing outcome to prostate cancer; using the competing-risks extension of the Cox proportional hazards models, as proposed by Fine and Gray.²⁸ To assess whether the association between GGT and prostate cancer risk was modified by relevant individual level characteristics, we performed subgroup analyses using interaction tests to assess statistical evidence of any differences in hazards. All statistical analyses were conducted using Stata version 13 (Stata Corp, College Station, Texas).

Results

Baseline characteristics

Table 1 summarizes baseline characteristics of the 2,390 participants included in the present analysis. The mean age of the participants was 53 (standard deviation, 5) years. Median (interquartile range) GGT value was 15 (20-33) U/L. Except for age, SES, history of diabetes, current smoking, fasting plasma glucose, and CRP, there were no significant differences in baseline characteristics between prostate cancer cases and controls.

Correction for within-person variability in GGT

Repeat measurements of GGT were taken 4 and 11 years after the baseline measurements during the follow-up period in a random sample of 725 participants, yielding a total of 1,450 repeat measurements of GGT. Overall, the age-adjusted RDR of loge GGT was 0.69 (95% CI: 0.63 to 0.74), which suggests that the association of GGT with prostate cancer using one-off or baseline measurements of GGT could underestimate the risk by $[(1/0.69)-1]*100 = 45\%$.

Gamma-glutamyltransferase and risk of prostate cancer

During a median (interquartile range) follow-up of 24.6 (16.8-26.9) years, 230 cases of prostate cancer (annual rate 4.52/1000 person-years at risk, 95% CI: 3.98 to 5.15) were recorded. A nonlinear association was observed between circulating GGT and prostate cancer risk (**Figure 1**). Comparing the top quartile versus combined bottom quartiles 1-3 of GGT, the age-adjusted HR for prostate cancer was 1.43 (95% CI: 1.07 to 1.93; $P=0.017$), which remained consistent 1.46 (95% CI: 1.06 to 2.02; $P=0.020$) following further adjustment for risk factors for prostate cancer. The results remained unchanged on additional adjustment for total energy intake, socioeconomic status, physical activity, and CRP 1.50 (95% CI: 1.08 to 2.07; $P=0.015$). After correction for within-person variability in GGT values, the similarly adjusted HRs were 1.68 (95% CI: 1.10 to 2.58; $P=0.017$), 1.74 (95% CI: 1.09 to 2.76; $P=0.020$), and 1.79 (95%

CI: 1.12 to 2.87; $P = 0.015$) respectively (**Table 2**). A total of 558 CVD deaths occurred during follow-up. In analyses including CVD death as a competing risk event, the HRs were 1.40 (95% CI: 0.98 to 1.99; $P = 0.067$) and 1.62 (95% CI: 0.97 to 2.72; $P = 0.067$) comparing the top quartile versus combined bottom quartiles 1-3 of baseline and usual GGT values respectively. The associations generally did not vary significantly by levels or categories of several clinically relevant characteristics and other risk markers (P for interaction ≥ 0.10 for each; **Figure 2**). A subgroup analysis could not be performed for diabetes status, because only three men with a prevalent history of diabetes developed prostate cancer during follow-up (**Table 1**).

Discussion

In this population of apparently healthy middle-aged Finnish men, we have shown that high values of GGT were nonlinearly and independently associated with an increased risk of prostate cancer over long-term follow-up. Analysis correcting for within-person variability in GGT values suggested that the association using baseline measurements of GGT with prostate cancer risk was almost half as strong as it otherwise would be using usual levels of GGT. Given the high CVD mortality rate in our study cohort which might have hindered our event of interest, the association between GGT and prostate cancer was less robust when CVD death was adjusted for as a competing risk event. This was not a surprising finding as GGT was independently associated with CVD mortality in the cohort. The association between GGT and prostate cancer remained generally consistent across several clinically relevant characteristics.

Comparison with previous studies

Several large-scale observational cohorts studies based in general population settings have shown an increased risk of overall and site-specific cancers with elevated circulating serum GGT activity. In a cohort of over 500,000 individuals within the Swedish AMORIS prospective study, elevated GGT was shown to be associated with an increased risk of developing overall and several site-specific cancers.¹⁴ In

in a large population-based cohort of 79,279 healthy Austrian men, Strasak and colleagues demonstrated GGT to be significantly associated with overall cancer risk as well as cancers of the digestive, respiratory, and urinary organs.²⁹ To provide a better indication of the relevance of GGT to cancer risk, given the inconsistencies in some of these previous studies; our group has recently conducted a pooled comprehensive analysis of available published prospective evidence on these associations in one comprehensive analysis.⁸ We showed that elevated GGT activity was associated with an increased risk of overall cancer, cancers of male genital organs, and cancers of digestive organs. In addition, it was demonstrated that the relationship of GGT with overall cancer risk was consistent with a log-linear shape. There are however limited published data on the associations of GGT and prostate cancer risk. To our knowledge, only two studies have evaluated the association; Tsuboya and colleagues found no evidence of an association between GGT and prostate cancer in their cohort of Japanese adults aged 40-79 years.³⁰ Van Hemelrijck and colleagues in the Swedish AMORIS prospective cohort study, found no evidence of an association between GGT modelled as a categorical variable and prostate cancer risk.¹⁴ However, when a linear relationship was assumed, a weak association was demonstrated. In stratified analysis, the authors also observed a stronger risk between GGT and prostate cancer in men with higher glucose levels, which was not observed in this study. In contrast, we were able to assess the shape of the GGT-prostate cancer relationship and observed a nonlinear relationship. Given the nonlinear shape of the association, GGT was modelled as a categorical variable and the findings showed evidence of an association between elevated GGT and an increased risk of prostate cancer. A subsidiary analysis using GGT as a continuous variable also showed evidence of statistically significant associations (data not shown but available on request).

Possible Explanations for Findings

It is uncertain if GGT has a direct role in the aetiology of prostate cancer or may just be a marker of underlying pathology. Several potential mechanisms have been hypothesized. A broad body of evidence

suggests the role of chronic inflammation in prostate carcinogenesis.^{2,4} Multiple factors have been suggested to contribute to the chronic inflammation process within the prostate and these include infections, dietary factors, and hormonal changes.² Elevated GGT activity may contribute to the inflammatory process within the prostate, as it mediates interconversion of the glutathione-containing inflammatory mediator leukotriene C4 into leukotriene D4.³¹ Indeed, given the long follow-up between baseline measurements of GGT and the occurrence of prostate cancer in our study, there is a likelihood that the effects of inflammation on prostate cancer are mediated through a chronic process. However, our observed GGT-prostate cancer association was independent of CRP, a well-known marker of low-grade chronic inflammation; which may suggest that other processes apart from inflammation may underlie the aetiology. Gamma-glutamyltransferase has pro-oxidant properties³² and is a source of reactive oxygen species (ROS), which is known to be involved in cellular growth, proliferation, and apoptosis.^{33,34} The persistent production of ROS may contribute to prostatic cancer development, progression, or invasion. Gamma-glutamyltransferase activity has been demonstrated to be increased in malignant lesions and suggested to confer survival advantages on tumour cells.³⁵ Elevated GGT activity may also be linked to the increased risk of prostate cancer via hyperglycemia.³⁶ Van Hemelrijck and colleagues in their study, showed a relatively stronger risk of prostate cancer with elevated GGT activity in individuals with higher glucose levels.¹⁴ In our analyses, however, the observed association was independent of fasting glucose levels and there was also no evidence of effect modification by glucose levels. Finally, the link between GGT and prostate cancer may be via lifestyle and environmental factors such as alcohol consumption, diet, pollutants, and smoking; which influence circulating GGT activity³⁷⁻³⁹ and may have direct roles in carcinogenesis.^{40,41} Indeed in our study, stratified analysis by amount of alcohol consumption showed elevated GGT to be statistically significantly associated with prostate cancer risk in men who consumed more alcohol, but the results were not statistically significant for men who consumed less alcohol; however, there was no statistically significant evidence of effect modification. Several mechanistic pathways have been suggested to underlie the association between GGT and prostate cancer risk;

however, most of these factors were accounted for in our multivariate analyses, therefore it may be unlikely that some of these pathways or factors would be essentially involved in the pathophysiology. Further large-scale studies are needed to replicate these associations and the aetiopathogenic pathways postulated to underlie the association deserve confirmation in mechanistic studies.

Implications of Findings

Our study extends previous findings on the potentially deleterious role of increasing circulating GGT activity on future risk of several chronic disease outcomes.⁷⁻¹² We have demonstrated that GGT is also associated with an increased risk of prostate cancer in addition to overall cancer and several site-specific cancers in the general male population. Whether GGT is just a marker of underlying cancer risk, a putative risk factor for cancer risk, or causal therapeutic target, is still yet to be ascertained. Further investigation of any potential relevance of GGT in prostate cancer prevention strategies is warranted. In the absence of such evidence, individuals with persistent elevated circulating GGT detected during routine liver panel tests may need further clinical evaluation.

Strengths and Limitations

Several strengths of our study deserve mention. These include the large-scale population-based prospective cohort design with selection of participants who were representative of the general population; the high response rate and no loss to follow-up; and reliable ascertainment of prostate cancer outcomes using an established cancer registry which employs unique personal identification codes. We had information on a comprehensive panel of confounding factors which allowed adequate adjustment for several risk factors for prostate cancer. The mean follow-up period in this study was sufficiently long to ascertain the risk for prostate cancer and the first cases of prostate cancer only occurred six years after baseline examinations, which minimised reverse causation and selection biases. Serial measurements of GGT made within a subset of individuals over time were available, enabling correction for within-person

variability in GGT activity over the long period of follow-up. We employed comprehensive analyses which included assessment of the shape of the association and stratified analyses by several clinical relevant characteristics. The study findings need to be interpreted in light of the following limitations: (i) the study included only Caucasian men and therefore the results cannot be generalised other races; (ii) despite adjustment for a comprehensive panel of lifestyle and biochemical risk markers, there is still a potential for residual confounding given the observational nature of the study; and (iii) we were unable to evaluate effect modification by history of diabetes on the association due to the low number of prostate cancer cases in men with a history of diabetes.

Conclusions

Gamma-glutamyltransferase is positively and independently associated with future risk of prostate cancer in a middle-aged Finnish male population over long-term follow-up. Further research is needed to understand the mechanistic pathways involved and if GGT may have any potential relevance in prostate cancer prevention.

Acknowledgments

We thank the staff of the Kuopio Research Institute of Exercise Medicine and the Research Institute of Public Health and University of Eastern Finland, Kuopio, Finland for the data collection in the study.

Funding Sources

The Academy of Finland, Helsinki, Finland; Finnish Foundation for Cardiovascular Research, Helsinki, Finland, and Finnish Cultural Foundation, Helsinki, Finland, supported the Kuopio Ischemic Heart Disease Study. These sources had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Disclosures

None.

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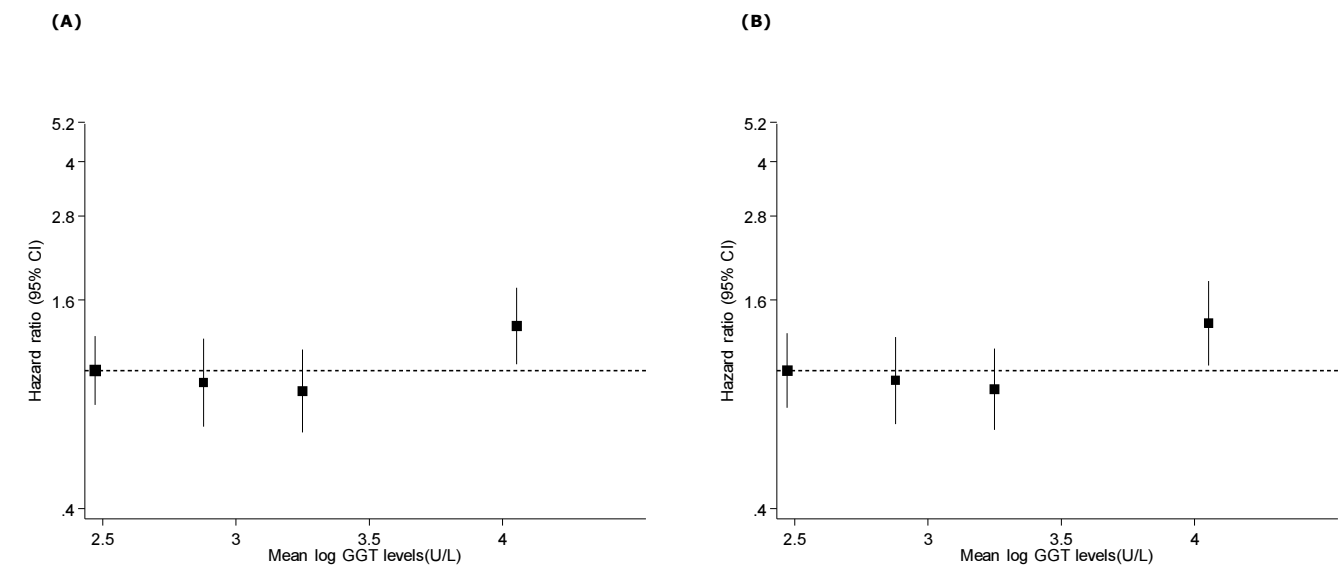
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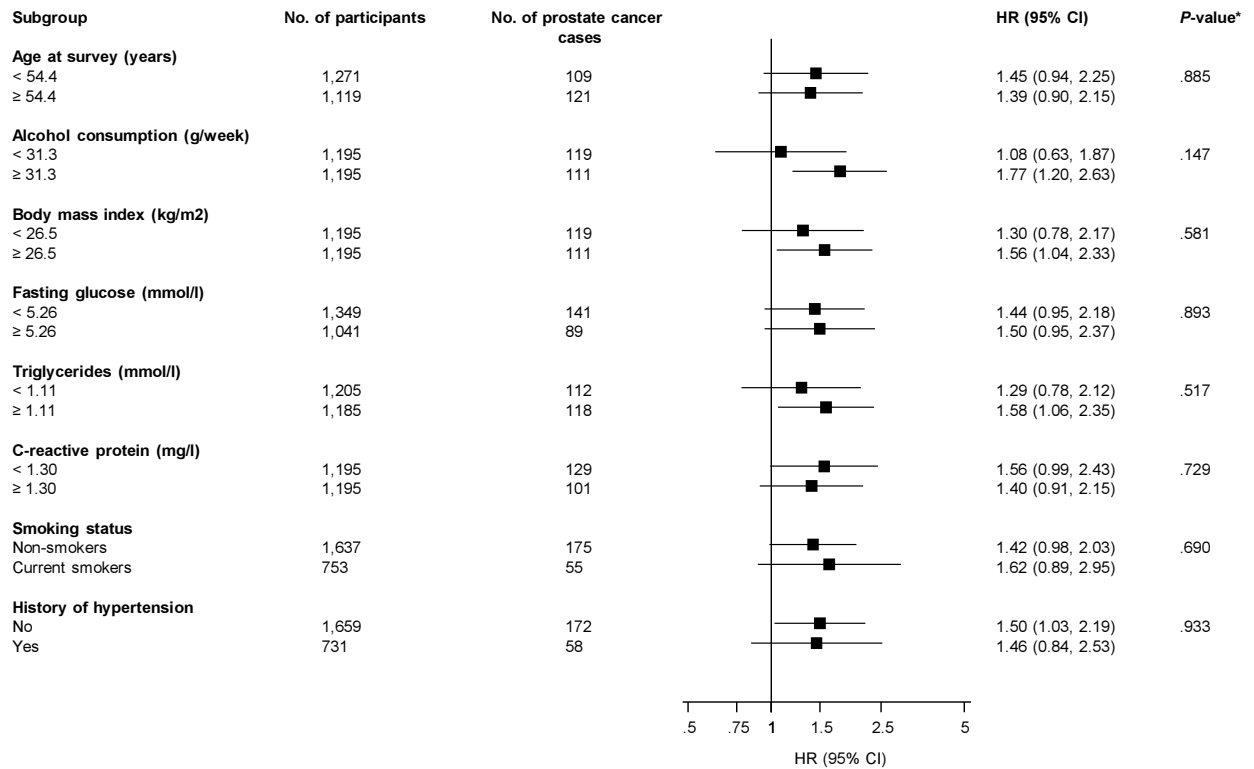
Figure legends

Figure 1. Hazard ratios for prostate cancer, by quartiles of baseline values of gamma-glutamyltransferase



A, adjusted for age; **B**, adjusted for age, body mass index, smoking status, history of diabetes, fasting glucose, triglycerides, total cholesterol, high-density lipoprotein cholesterol, and alcohol consumption

Figure 2. Hazard ratios for baseline values of gamma-glutamyltransferase and prostate cancer risk by several participant level characteristics



A, adjusted for age; **B**, adjusted for age, body mass index, smoking status, history of diabetes, fasting glucose, triglycerides, total cholesterol, high-density lipoprotein cholesterol, and alcohol consumption; CI, confidence interval; GGT, gamma-glutamyltransferase; HR, hazard ratio; *, *P*-value for interaction

Hazard ratios compare the top quartile versus combined bottom quartiles 1-3 of GGT

Table 1. Baseline Participant Characteristics

	Overall (N=2,390) Mean (SD) or n (%)	Without prostate cancer (N=2,160) Mean (SD) or n (%)	With prostate cancer (N=230) Mean (SD) or %	P-value
Log _e GGT (U/L)	3.13 (0.65)	3.13 (0.65)	3.14 (0.67)	0.768
Questionnaire/Prevalent conditions				
Age at survey (years)	53.2 (5.0)	53.1 (5.0)	53.9 (4.5)	0.019
Alcohol consumption (g/week)	74.6 (134.7)	75.3 (137.9)	68.2 (98.7)	0.446
Total energy intake, kJ/day	9,853 (2,589)	9,835 (2,591)	10,023 (2,566)	0.295
Socioeconomic status	8.54 (4.23)	8.63 (4.21)	7.75 (4.34)	0.003
History of diabetes	96 (4.0)	93 (4.3)	3 (1.3)	0.028
Current smokers	753 (31.5)	698 (32.3)	55 (23.9)	0.009
History of hypertension	731 (30.6)	673 (31.2)	58 (25.2)	0.063
Physical measurements				
BMI (kg/m ²)	26.9 (3.6)	26.9 (3.6)	26.7 (3.1)	0.404
SBP (mmHg)	134 (17)	134 (17)	133 (15)	0.356
DBP (mmHg)	89 (11)	89 (11)	88 (10)	0.792
Physical activity (kJ/day)	1,546 (1,486)	1,527 (1,465)	1,727 (1,667)	0.053
Lipid markers				
Total cholesterol (mmol/l)	5.91 (1.09)	5.91 (1.09)	5.94 (1.10)	0.679
HDL-C (mmol/l)	1.30 (0.30)	1.29 (0.30)	1.31 (0.31)	0.697
Log _e triglycerides (mmol/l)	0.12 (0.51)	0.12 (0.51)	0.12 (0.52)	0.898
Metabolic and inflammatory markers				
Fasting plasma glucose (mmol/l)	5.36 (1.28)	5.38 (1.33)	5.77 (1.94)	0.033
Serum creatinine (μmol/l)	89.6 (20.8)	89.4 (21.5)	91.7 (70.7)	0.239
Log _e CRP (mg/l)	0.34 (0.97)	0.36 (0.99)	0.69 (1.01)	0.020

BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; GGT, gamma-glutamyltransferase HDL-C, high-density lipoprotein cholesterol; SD, standard deviation; SBP, systolic blood pressure;

Table 2. Associations of baseline and usual levels of gamma-glutamyltransferase with prostate cancer

Serum GGT (U/L)	Events/Total	Model 1		Model 2		Model 3	
		HR (95% CI)	<i>P</i> -value	HR (95% CI)	<i>P</i> -value	HR (95% CI)	<i>P</i> -value
Baseline GGT values							
Q1- Q3 (5-33)	170 / 1,826	ref		ref		ref	
Q4 (> 33)	60 / 564	1.43 (1.07 to 1.93)	0.017	1.46 (1.06 to 2.02)	0.020	1.50 (1.08 to 2.07)	0.015
Usual GGT values							
Q1- Q3 (5-33)	170 / 1,826	ref		ref		ref	
Q4 (> 33)	60 / 564	1.68 (1.10 to 2.58)	0.017	1.74 (1.09 to 2.76)	0.020	1.79 (1.12 to 2.87)	0.015

Model 1: Adjusted for age

Model 2: Model 1 plus BMI, smoking status, history of diabetes, fasting glucose, triglycerides, total cholesterol, high-density lipoprotein cholesterol, and alcohol consumption

Model 3: Model 2 plus total energy intake, socioeconomic status, physical activity, and C-reactive protein